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<p>(21) International Application Number: <b>PCT/GB97/03113</b></p> <p>(22) International Filing Date: <b>13 November 1997 (13.11.97)</b></p> <p>(30) Priority Data: 9623634.4                      13 November 1996 (13.11.96)    <b>GB</b></p> <p>(71) Applicant (for all designated States except US): <b>COLORCON LIMITED [GB/GB];</b> Flagship House, Victory Way, Crossways, Dartford, Kent DA2 6QD (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): <b>BROWN, Steven, Robert [GB/GB];</b> 2 The Willows, Kemsley, Sittingbourne, Kent ME10 2TE (GB). <b>REEVES, Linda, Ann [GB/GB];</b> 31 Hatton Court, Lubbock Road, Chislehurst, Kent BR7 5JQ (GB). <b>STANIFORTH, John, Nicholas [GB/GB];</b> High Trees, 170 Bloomfield Road, Bath BA2 2AT (GB).</p> <p>(74) Agents: <b>BARDO, Julian, Eason et al.;</b> Abel &amp; Imray, Northumberland House, 303-306 High Holborn, London WC1V 7LH (GB).</p>		<p>(81) Designated States: <b>AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO</b> patent (GH, KE, LS, MW, SD, SZ, UG, ZW), <b>Eurasian</b> patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), <b>European</b> patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), <b>OAPI</b> patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: <b>METHOD AND APPARATUS FOR THE COATING OF SUBSTRATES FOR PHARMACEUTICAL USE</b></p> <div data-bbox="446 1165 1153 1722"> </div> <p>(57) Abstract</p> <p>A method of coating a substrate includes applying an active coating material to the substrate to form an active coating layer. The active coating material comprises biologically active material and the active coating layer is removable from the substrate.</p>		

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Method and Apparatus for the Coating of Substrates for  
Pharmaceutical Use

The present invention relates to methods of coating substrates, to apparatus for coating substrates and to  
5 coated substrates for pharmaceutical use. In particular, but not exclusively, the invention relates to the coating of pharmaceutical substrates to produce solid dosage forms.

It is to be understood that the term "solid dosage  
10 form" is to be interpreted in a broad sense as covering a wide variety of pharmaceutical products. Thus the term covers pharmaceutical products to be taken orally, for example, pharmaceutical tablets of conventional shape as well as capsules and spherules and tablets of unconven-  
15 tional shape. The term also covers pharmaceutical products not taken orally, for example, a pessary, a bougie, a suppository or a patch for application to the skin. Also, where reference is made to "pharmaceutical substrate" it is to be understood that the term covers  
20 the substrates of the solid dosage forms indicated above. The term "solid dosage form" does not, however, include pharmaceutical products such as small pellets and granules, for example small pellets which are filled into capsule shells for administration and granules which are  
25 compressed to form tablets; such pellets or granules are not themselves each solid dosage forms but rather, when combined together in a capsule or tablet, define in combination a solid dosage form.

It will be understood that the term "active  
30 material" and "active component" used throughout the specification includes material which is biologically active and will comprise one or a mixture of pharmaceutical materials. The pharmaceutical materials include those materials which are administered for the  
35 prevention and/or treatment of disease.

Active materials are conventionally administered in the form of tablets.

In a conventional method of producing a pharmaceutical tablet, a mixture containing the  
5 biologically active ingredient together with diluents such as lactose and other ingredients is mixed and portions of the mixture are formed into discrete tablets by, for example, pressing samples of the mixture.

A problem with the method of producing tablets  
10 described above is that, due to inhomogeneity of the mixture from which the tablet cores are made, the amount of active ingredient in the resulting tablet cores varies from one tablet to the next. While that is a problem for all types of tablet core produced in that  
15 way, it is a particularly serious problem when the amount of active ingredient in each core is low, for example for active compounds of high activity. In that case a small absolute variation in the percentage amount of active  
20 variation in the dose contained in each tablet which is clearly most undesirable.

In one known method, a coating solution containing active material is applied to the surfaces of small beads using conventional spray coating techniques, for example  
25 by spraying the coating solution towards the beads as they are tumbled in a revolving drum. The coated beads are filled into capsule shells for administration. Such a method is not appropriate for use where accuracy in the amount of the active material applied to the cores is  
30 required because there is little control over the amount of coating material applied to each core using that method.

Active components are often administered in tablet form. As indicated above, conventional tablets include a  
35 small amount of active component and a large amount of diluent such as lactose so that the tablet is a convenient size. The tablet is a convenient way for the

active component to be administered because each tablet contains a predetermined metered dose of the active material.

However, some patients find the taking of tablets difficult, for example because of their size or because of the presence of the other ingredients in the tablet composition. Thus an alternative dosage form would be desirable.

GB 1 561 100 describes the coating of a web with material containing an active ingredient. The coated web is processed to internalize the active coating by, for example, lamination and winding to provide a dosage form.

It is an object of the invention to overcome or mitigate one or more of the above mentioned disadvantages.

In accordance with the invention, there is provided a method of coating a substrate, the method including the steps of applying an active coating material to the substrate to form an active coating layer, the active coating material comprising biologically active material, wherein the active coating layer is removable from the substrate.

In accordance with the invention, the active material is applied as a coating to a substrate from which it can be removed.

In one alternative embodiment of the invention, the coating material is applied directly onto a surface of the coating apparatus, the coating formed in the process being removed from the apparatus as a wafer containing the active material.

In a second alternative embodiment of the invention, the coating material is applied onto a substrate, the coating being removed from the substrate as a wafer, for example by a patient prior to the administration of the material. The substrate may be, for example, a sheet comprising plastics material, for example low adhesion plastics material.

The surface of the substrate may be precoated with one or more coating layers.

Preferably, the active coating material is applied electrostatically. There are various advantages in  
5 applying coating materials electrostatically, for example, reduction in waste of coating material, improved coating efficiency and improved coating weight uniformity.

In one alternative of the invention, the active  
10 coating material is applied in the form of a dry powder.

Advantageously, at least 90% by weight of the particles of the active coating material have a particle size less than 200 $\mu$ m.

Advantageously, at least 90% by weight of the  
15 particles of the active coating material have a particle size between from 1 to 200 $\mu$ m. Preferably, at least 90% by weight of the particles of the active coating material have a particle size between from 1 $\mu$ m to 100 $\mu$ m. The term "particle size" refers to the equivalent particle  
20 diameter of the particles and may be measured using, for example, laser light diffraction. The particle size of the powder is an important factor in powder coating techniques. If the particles of the powder are very small, the powder will often be too cohesive for  
25 successful powder application using many powder coating techniques. However, large particles can be disadvantageous because they are often more difficult to coat onto a surface and, if the coating material is to be fused after application to the surface, longer fusing  
30 times may be required, leading to increased risk of damage to the substrate and to the active component.

Where reference is made to % by weight of particles, for example the % by weight of particles having a particular size, the particles will also preferably have  
35 that % by volume of particles of that size.

Alternatively, the coating material may be applied in the form of a liquid.

Advantageously, the active coating material further includes one or more excipients. The formulation will usually consist of the active component and a mixture of excipients that will aid in the coating of the material.

5 The formulation may also include other components, for example, colorants and/or flavourings and/or agents to control the rate of release of the active component.

Advantageously, the substrate is conveyed through a region adjacent to a source of the active coating  
10 material. That allows the method to be continuous.

In one advantageous embodiment of the invention, the method comprises supporting the substrate adjacent to the source of the active coating material with a surface of the substrate maintained at such a different electric  
15 potential from that of the active coating material that the application of the electric potential causes the active coating material to move from the source of the active coating material towards the substrate, a surface of the substrate becoming coated with the active coating  
20 material.

Preferably, the substrate is supported from above and the powder moves from the source upwards towards a lower surface of the substrate.

Preferably, the substrate is charged when the  
25 substrate is adjacent the source of the active coating material. Alternatively, or in addition, the source of active coating material may be charged.

The method may further include the step that after the active coating layer is applied the active coating  
30 material is treated to form an active film coating secured to the surface of the substrate. Where the coating material is in the form of a powder material, the treatment advantageously comprises a heating step, preferably by infra red radiation, but other forms of  
35 electromagnetic radiation may be used. Usually, the change in the coating upon heating will simply be a physical change from a powder to a liquid and then, on

cooling, to a solid coating, but there are other possibilities: for example, the powder coating may comprise a polymer which is cured during the treatment step, for example by irradiation with energy in the gamma, ultra violet or radio frequency bands, to form a cross-linked polymer coating.

The method may further include the step of applying a cover coating layer onto the active coating layer to form a cover coating layer such that the active coating layer is substantially completely covered by the cover coating layer.

The active coating material applied to the surface of the substrate might not be treated to form an active film coating. A cover coating layer applied subsequently over the active coating material could be used to seal the active coating on the surface of the substrate.

Where the coating material is in the form of a liquid, the treatment advantageously comprises drying the coating material with a heater although other methods could be used.

The coating material containing the active component is susceptible to damage at high temperatures and it is therefore particularly important that the temperature of treatment is not high. Advantageously, the temperature of treatment is less than 250°C, preferably less than 200°C and more preferably less than 150°C. Where the higher treatment temperatures are used, the duration of the treatment is advantageously short to reduce the possibility of damage of the coating material.

Preferably, the cover coating material is applied electrostatically. The cover coating material may be in the form of a powder. The cover coating material may also include active material. The active material in the cover coating may be the same as or different from the active material in the active coating layer.

Advantageously, at least 90% by weight of the particles of the cover coating material have a particle



size between from 1 to 200 $\mu$ m.

Preferably, the substrate is conveyed through a region adjacent to a source of the cover coating material.

5 In one advantageous embodiment of the invention, the method comprises supporting the substrate adjacent to the source of the cover coating material with a surface of the substrate maintained at such a different electric potential from that of the cover coating material that  
10 the application of the electric potential causes the cover coating material to move from the source of the cover coating material towards the substrate, a surface of the substrate becoming coated with the cover coating material.

15 Advantageously, the substrate is supported from above and the powder moves from the source upwards towards a lower surface of the substrate.

Preferably, the substrate is charged when the substrate is adjacent to the source of the cover coating  
20 material. Alternatively, or in addition, the source of cover coating material may be charged.

Advantageously, the method further includes the step that after the cover coating layer is applied the cover coating material is treated to form a film coating  
25 secured to the surface of the substrate. The treatment of the cover coating layer may be similar to that of the active coating layer described above.

In an embodiment of the invention the active coating layer covers only part of a surface of the substrate. In  
30 that embodiment, the cover coating layer may cover only part of a surface of the substrate, or alternatively may cover the whole surface of the substrate.

The cover coating layer may be applied by depositing powder which thereafter forms a layer over the active  
35 coating layer or by applying a preformed sheet or film over the active coating layer.

The method may further include the step of applying

a further coating material to a surface of the substrate to form a further coating layer. The further coating material may include biologically active material, the further coating layer forming a further active coating layer and the method may further include the step of applying a further cover coating material onto the further active coating layer to form a further cover coating layer such that the further active coating layer is substantially completely covered by the further cover coating layer.

Thus substrates having two or more different active components may be produced. The cover coating material covering the first active coating may be different from that covering the second active coating so that the rate of release of the first active component may be different from that of the second active component. Alternatively, the two active components may be the same and the cover coatings may be the same or different materials. One or more of the cover coating materials may contain active material.

Advantageously, the method is continuous. In practice, there are considerable advantages in being able to operate the coating process continuously rather than as a batch process.

Advantageously, the active coating material is applied to a part of a surface of the substrate, the active coating layer forming a first active coated region on the surface of the substrate. Where, for example, a plurality of coating layers are to be applied to each substrate, each coating layer forms a coated region on a part of the substrate.

Thus the method may include the further step of applying a second active coating layer onto a surface of the substrate, the second active coating layer forming a second active coated region on a surface of the substrate.

Preferably, the method further includes the step of

applying a cover coating material onto the active coating layer to form a cover coating layer such that the active coating layer is substantially completely covered by the cover coating layer and such that the cover coating layer is removable from the substrate. Depending on the nature of the cover coating material, the cover coating layer may be removable together with the active coating layer or may be removable separately. The cover coating layer provides a cosmetic coating and may also protect the active coating material. The cover coating material may also include active material which may be the same as or different from the active material of the active coating layer. The cover coating may comprise a preformed film or sheet of material which is applied over the active coating.

Where more than one active coating layer is applied to the substrate, the method preferably further includes the step of applying a second cover coating layer onto the second active coating layer to form a second cover coating layer such that the second active coating layer is substantially completely covered by the second cover coating layer, the second cover coating layer being substantially separate from the first cover coating layer.

The invention also provides a method of coating a plurality of coating regions onto the surface of a substrate, the method comprising the steps of:

(a) applying active coating material to a surface of the substrate to form a plurality of active coating regions on the surface comprising active coating layers, the active coating material including biologically active material

(b) applying cover coating material to a surface of the substrate to form a plurality of cover coating regions, the cover coating regions forming layers of cover coating material, each active coating region being substantially completely covered by a cover coating

region,  
such that each region of active coating and cover coating  
is removable from the surface of the substrate.

Advantageously, the method further includes the step  
5 of removing that active coating layer from the substrate  
to form a wafer comprising active material. Each wafer  
may comprise a single dose of active component.  
Alternatively, the wafer may be subsequently cut to form  
wafer portions, each wafer portion including  
10 substantially a dose of active material.

Where reference is made to the quantity of active  
coating material being substantially equal to a dose of  
the active material, it will be understood that the  
quantity may be a fraction of the single standard dose,  
15 for example  $1/2$  or  $1/3$  of a single standard dose of the  
active material. It will be understood that the quantity  
of active material will depend on the active component  
used and the number of solid dosage forms to be taken by  
the patient for each dose. Where more than one layer of  
20 the active coating material is to be applied to each  
substrate, the quantity of active component in each layer  
will be chosen accordingly.

The invention also provides apparatus for coating a  
substrate according to a method as described above.

25 The first aspect of the invention also provides an  
apparatus for coating a substrate, the apparatus  
comprising:

- (a) a source of active coating material,
- (b) support means for supporting a substrate
- 30 adjacent to the source of the active coating material  
such that the active coating material forms an active  
coating layer on a surface of the substrate.

Advantageously, the apparatus further comprises:

- (c) a source of a cover coating material,
- 35 (d) means for conveying the substrate having the  
active coating layer to a position adjacent to the source  
of cover coating material such that the cover coating

material forms a cover coating layer which substantially completely covers the active coating layer.

The apparatus advantageously includes means for applying the active coating material and/or the cover  
5 coating material electrostatically. As indicated above, the coating material may be applied in the form of a dry powder or in the form of a liquid.

Advantageously, the substrate comprises a conveyor belt.

10 Advantageously the apparatus further includes means for applying a charge to the source of active coating material. The charge can be adjusted to change the amount of coating material applied to the substrate.

Advantageously, the apparatus further includes  
15 charging means for applying a charge to the substrate. The charge may be applied using a corona charge wire adjacent to the substrate or by arranging a charged plate adjacent to the substrate. The charged substrate attracts coating material from the source onto the  
20 surface of the substrate. Thus it is possible to obtain a very thin uniform layer of coating material on the substrate surface.

Preferably, the source is arranged below the conveyor.

25 Also provided by the present invention is an apparatus for coating a substrate, the apparatus comprising:

- (a) a source of coating material
- (b) means for moving the substrate relative to the  
30 source of coating material,
- (c) means for applying an active coating material onto a surface of the substrate to form a plurality of active coating regions,
- (d) means for applying a cover coating material  
35 onto the surface of the substrate to form a plurality of cover coating regions such that each active coating region is substantially completely covered by a cover

coating region,  
the coating materials being applied such that the active  
coating material is removable from the surface of the  
substrate.

5       The invention also provides a coated substrate  
comprising an active coating layer on a surface of the  
substrate, the active coating layer including  
biologically active material and in which the active  
coating layer is removable from the surface of the coated  
10       substrate.

      In one embodiment of the invention, each active  
coating layer comprises a quantity of biologically active  
material which is substantially equal to one dose or, for  
example, one half dose of the biologically active  
15       material. It will be understood that the quantity of  
active component will depend on the active material used  
and the required dose.

      Alternatively the active coating layer may  
subsequently be cut into small portions.

20       Preferably, the substrate further includes a cover  
coating layer on a surface of the substrate, the cover  
coating layer substantially completely covering the  
active coating layer in which the cover coating layer is  
removable from the surface of the substrate. As  
25       indicated above, the cover coating layer may be removable  
separately from the active coating layer.

      The substrate may include a plurality of active  
coating layers forming active coating regions on a  
surface of the substrate.

30       Preferably, each active coating region includes a  
cover coating region comprising a layer of cover coating  
material in which each active coating region is substan-  
tially completely covered by a cover coating region.

      In one alternative embodiment of the present  
35       invention, for example where the active coating material  
is applied as a liquid, the active coating material is  
applied as a metered dose to a surface of the substrate,

to form an active coating layer on the surface.

Very accurate application of the coating material on each surface can be obtained.

This is to be contrasted with the known methods  
5 where coating material is sprayed towards the cores. In that case the amount of coating material applied to each substrate depends on many factors all of which would require close control if accurate application is to be achieved. It will be understood that whilst reference is  
10 made to applying a metered dose, that should not be taken to imply that there is necessarily any measurement of the amount of material applied. A metered volume of liquid may be applied to each substrate.

Advantageously, a predetermined number of droplets  
15 of active coating material are applied to the surface of the substrate. Thus where the droplets are of the same size, the number of droplets applied to the substrate surface determines the amount of active material applied. By altering the number of droplets applied, the apparatus  
20 can easily be adapted to apply the required quantity of active material.

Advantageously the coating method is such that the coefficient of variation of the quantity applied to each substrate or region of the substrate is not more than  
25 15%.

As indicated above, where the coating material includes active material, the accuracy and reproducibility of the application of the material to the substrates is of particular importance. For known  
30 spraying techniques such as those described above, the coefficient of variation can be 50% or more. Whilst that is acceptable where the coating is a cosmetic coating, it is not acceptable where the coating contains active material. Preferably the coefficient of variation is not  
35 more than 10%, and most preferably 3% or less.

Advantageously, the active coating material is applied in the form of individual liquid droplets which

are propelled from the supply directly towards a surface of the substrate.

As indicated above, where the material is applied as a plurality of individual droplets, it is more simple to  
5 alter the dose of active material applied to the substrate by changing the number of droplets applied. Thus advantageously, the number of droplets applied is controllable.

An ink jet head may be used in the coating of the  
10 substrates with active coating material. A conventional ink jet head, for example those used for ink jet printers, can be used to apply an easily controllable amount of material from the head onto a substrate.

In one embodiment of the invention, the area of the  
15 surface of the substrate covered by the active coating layer is less than 40% of the total surface area of the substrate. The area covered by the active coating layer may be less than 25% of the total surface area of the substrate. The active coating may form a plurality of  
20 small coated regions on the surface of the substrate.

Thus the active coating layer may cover only a part of the exposed surface of the substrate.

Where the quantity of active material to be administered using each solid dose is small, as indicated  
25 above, it is advantageous for the proportion of active component in the active coating material to be large.

By covering a smaller proportion of the surface of the substrate, a smaller amount of coating material may be used. Thus the proportion of active component in the  
30 coating material may be increased.

The active coating material may be applied to a plurality of individual regions of the surface of the substrate.

The invention also provides a method of coating a  
35 substrate, the method comprising applying an active coating material to a surface of the substrate to form an active coating layer, the active coating material



comprising biologically active material, applying a cover coating over the exposed surfaces of the active coating layer and dividing the substrate to form substrate portions, each substrate portion including substantially one dose of the active material.

The invention also provides a pharmaceutical solid dosage form comprising a substrate and an active coating layer covering less than 25% of the surface area of the substrate the active coating layer comprising biologically active material.

The coating layer may be shaped, for example to form a pattern, a picture, symbols, letters or numerals.

The invention also provides a wafer for administration to a patient, the wafer comprising biologically active material and having a thickness of less than 2mm. Preferably the thickness is less than 1mm.

The invention further provides an intermediate product for use in producing a plurality of solid dosage forms, the intermediate product comprising a substrate and an active coating layer deposited on the substrate, the amount of active coating material deposited on a given area of the substrate being controlled such that the product can subsequently be divided into portions with each portion containing a predetermined amount of active coating material, each predetermined amount being one dose of the active material.

In accordance with a further aspect of the invention, there is provided a method of coating a substrate, the method comprising applying an active coating material to a surface of the substrate to form an active coating layer, the active coating material comprising biologically active material, applying a cover coating layer over the exposed surfaces of the active coating layer and dividing the layered product to form layered portions, each layered portion including substantially one dose of the active material.

In accordance with the further aspect of the invention, the active coating material can be such that it is not removed from the substrate. For example, the active material might be applied to an edible film which  
5 can be administered orally.

It will be understood that the method of coating may further include features of the method of the first aspect of the invention described herein. Furthermore, it will be appreciated that the apparatus and coating  
10 materials described in respect of the first aspect of the invention could be used in the method in accordance with the further aspect of the invention, with minor modifications where necessary.

Embodiments of the invention will now be described  
15 by way of example having reference to the drawings of which:

- |             |   |
|-------------|---|
| Figure 1    | shows schematically a side view of an apparatus for coating a tablet core;                                      |
| 20 Figure 2 | shows schematically a side view of a part of the apparatus of Figure 1; and                                     |
| Figure 3    | shows schematically a side view of an apparatus for coating a substrate<br>25 in accordance with the invention. |

The apparatus shown in Figure 1 is for coating both faces of pharmaceutical tablet cores. The apparatus comprises an inclined tablet core feed chute 1 leading to a first rotatable wheel 2 having circular depressions 3  
30 in its outer surface. The cores 4 are fed from the chute 1 into the depressions 3 where they are held by suction by means of a suction line 5 in communication with the base of the depression 3 via an opening. The first drum is rotated in the direction shown by the arrow A.  
35 Adjacent to the outer surface of the wheel 2 downstream from the feed chute 1 is an active coating station 6 and a cover coating station 7. Downstream from the active

coating station is an active coating fusing station 8 at which the active coating is fused and downstream from the cover coating station 7 is a cover coating fusing station 9 at which the cover coating is fused. A cooling station 5 (not shown) may be provided downstream from each of the fusing stations 8, 9 where cool air is directed at the core to cool the fused coating.

A second wheel 10 similar to the first wheel 2 is arranged adjacent to the first wheel 2, the nip between the wheels being downstream of the fusing station 9. The second wheel 10 rotates in an opposite sense to that of the first wheel 2 as shown by the arrow B. Arranged adjacent to the outer edge of the second wheel 10 downstream from the nip of the two wheels are a second cover coating station 11 and a second fusing station 12.

Figure 2 shows the active coating device 6 in more detail. Figure 2 shows a portion of the wheel 2 together with a core 4 in a depression 3 on the surface of the wheel 2. As described below, the apparatus of Figure 2 can be used to form wafers of coating material in accordance with the present invention.

The active coating station 6 comprises a conveyor 13 arranged in a loop in a vertical plane so that the upper surface 14 faces the surface of the wheel and the cores 4 which pass the device 6 as the wheel rotates. The contour of the upper surface 14 of the conveyor 13 is chosen to match the contour of the outer surface of the wheel so that the distance between the core and the upper surface of the conveyor is unchanged as the wheel rotates. The direction of rotation C of the conveyor 13 is such that the direction of movement of the upper surface of the conveyor is opposite to that of the movement of the core over the upper surface of the conveyor. Alternatively, the direction of movement of the upper surface of the conveyor and the core may be the same.

As shown in Figure 2, a corona charge wire 15 and

powder source 16 are arranged beneath the conveyor immediately below the lower surface 17 of the conveyor.

The corona charge wire 15 sprays charge onto the lower surface 17 of the conveyor. It will be appreciated  
5 that a different method could be used to apply charge to the conveyor.

The powder source 16 uses an archimedes screw to form a small mound of powder beneath the lower surface of the conveyor. The source 16 comprises a hopper 18  
10 containing the powder including the biologically active component, and an Archimedes screw 19 which in use passes through the powder material 20 in the hopper 18 and through a vertical barrel 21. Thus, the powder material 20 is circulated from the lower regions of the hopper 18  
15 to the top of the barrel 21 where a moving heap of powder is formed. The heap will be of substantially constant size and shape as excess powder overflows from the top of the barrel 21 and is returned to the hopper 18.

Stirrers 22 are provided in the hopper 18 to help to  
20 improve the flow of the powder and break up any agglomerates.

Thus a small moving heap of powder of substantially constant size and shape is formed beneath the lower surface of the conveyor 17.

25 It will be appreciated that a device other than the Archimedes screw could be used to form the heap of powder.

The powder source 16 is located downstream from the charge spraying device 15 and powder from the heap of  
30 powder is attracted to the surface of the charged conveyor 17 where it forms a thin, uniform layer which is transported to the upper surface 14 of the conveyor.

The tablet core 4 passing over the upper surface of the conveyor is held at a different potential from that  
35 of the conveyor 13, either by earthing the core or applying a charge to the core, and powder on the conveyor moves from the conveyor to the exposed surfaces of the

tablet core 4 to form a powder coating.

The active coating station 6 is enclosed in a housing (not shown) to reduce the risk of powder loss of the active powder. In use the housing has an opening  
5 above the upper surface of the conveyor 14 so that the tablet core 4 is exposed to the active powder coating material as it passes the station 6.

It will be appreciated that the thickness of the powder layer formed on the surface of the tablet core  
10 depends on several factors including the amount of charge sprayed onto the conveyor, the magnitude of the charge applied to the core, the size of the heap of powder produced, the size of the opening in the housing and the speed of the conveyor. Those factors will be varied to  
15 give the desired coating depending on the type of powder and core used.

The composition of the active coating material used will of course depend on the active ingredient to be used and the amount of the coating to be applied.

20 Active materials most suitable to be applied to the tablet include those materials having a high therapeutic activity, for example those where the usual prescribed dose is about 1mg or less, and which have a good stability to degradation due to heat where the coating  
25 material containing active material is to be heated.

An active material which may be applied to a tablet core in accordance with the invention is Diltiazem HCL.

The amount of active ingredient to be coated onto each core or other substrate will generally be small and  
30 the active ingredient will usually be diluted with one or more excipients. The excipients used will be chosen so that they aid the coating of the active material onto the cores by, for example improving the electrostatic properties of the powder and its physical properties and  
35 aiding the formation of the fused active coating, for example the excipient may be a material which melts at a low temperature to aid the formation of a film.

Where the active coating material is a powder, the particle size will be an important factor with regard to the transfer of the active coating material from the conveyor to the tablet core and to the subsequent fusing of the material. Usually a particle size range of 1 to 200 $\mu$ m will be used (at least 90% of the particles of the powder having a size within that range).

One example of an active coating material is as follows:

10	Xylitol	45% wt
	Diltiazem HCL (active)	45% wt
	TiO <sub>2</sub>	9% wt
	Colloidal silica	1% wt

It is thought that in at least one embodiment of the invention, the active composition will comprise three main components together with additives.

The components may, for example, comprise the following

- i) a continuous phase component, for example Xylitol or PEG 6000,
- ii) the active component,
- iii) a particle seed and/or charge modifying component, for example TiO<sub>2</sub> or silica,
- iv) a flow aid, for example colloidal silica or magnesium stearate.

Each component may comprise one or more different materials.

The active coating material of the above example was in the form of a powder and had a particle size distribution such that at least 90% wt of the particles had a size in the range of from 5 to 25 $\mu$ m.

It is often preferred that at least 90% by weight of the particles have a size in the range of from 1 to 45 $\mu$ m. In one preferred embodiment 90% by weight of the particles have a size less than 70 $\mu$ m, 50% by weight have a size less than 40 $\mu$ m and 10% by weight of the particles have a size less than 10 $\mu$ m.

The active powder coating material may be produced using one or a combination of the following processing steps:

- a) precipitation of two or more of the components to  
5 form composite particles
- b) spray drying of two or more of the components to  
form composite particles
- c) granulation
- d) extrusion
- 10 e) micronisation.

For example, all of the components of the composition may be co-micronised to give a powder material having the desired particle size.

An example of a powder cover coating material is as  
15 follows:

	39.75%	Eudragit RS (ammonio-methacrylate copolymer)
	39.75%	Klucel (hydroxy propyl cellulose)
20	15.0%	Titanium dioxide
	5.0%	Aluminium lake
	0.5%	Aerosil 200 (colloidal silicon dioxide)

The cover coating material was prepared by the  
25 following method:

- a) A sample containing the % wt of components listed above was premixed in a high shear mixer. Water was added to the mixture in a high shear mixer for a few minutes to give a granulated mixture which was dried in a  
30 fluid bed drier at a temperature of about 45°C for 20 to 30 minutes to give a material having a moisture content (measured as loss on drying) below 3% by weight. The material was impact milled and then micronised using a  
35 fluid energy mill to a powder containing particles having a size distribution such that 50% by volume of particles were of a size less than 20µm.

The cover coating material will usually include

components to control the dissolution rate of the cover coating to give controlled release of the active material in the active coating layer. Where more than one active coating is applied to each tablet or substrate, the release of each active coating can be different where different materials are used for the cover coating over each of those active coatings.

Where one or more of the coatings are applied as liquid coatings, a suitable liquid coating device would be used at the active coating station 6 and/or the cover coating station 7 and the fusing device would be replaced by, for example a drying device to dry the liquid coating, if necessary.

In an embodiment of the invention an apparatus similar to that shown in Figure 2 is used to form wafers of coating material.

The apparatus comprises a conveyor belt of chemically inert material having a Teflon (RTM) coating. A corona charge wire is arranged immediately below the lower surface of the conveyor and sprays charge onto the lower surface. A powder source similar to that shown in Figure 2 is also arranged beneath the lower surface of the conveyor downstream of the corona wire. The powder material in the powder source contains an active component and may have similar composition to the active powder described above. Preferably a higher proportion of film-forming components are added to the powder, for example hydroxypropylcellulose (HPC).

An example of an active coating material is as follows:

Eudragit RS	23%
Diltiazem HCL (active)	40%
HPC	25%
TiO <sub>2</sub>	7%
PEG 4000	5%

The amounts of the components are expressed as



percent by weight.

Powder from the powder source is attracted to the surface of the charged conveyor where it forms a thin, uniform layer of powder on a part of the outer surface of the conveyor belt. A heater is positioned downstream of the powder source and the heater fuses the powder material on the conveyor surface to form a fused film coating on the surface. The film coating is conveyed on the conveyor to a region where it is removed as a thin strip of film.

A cooling station may be positioned downstream of the heater to cool the film coating. The film strip removed from the conveyor may be passed to a cutting station where it is divided into portions, each of which may contain a dose of active material.

In an alternative embodiment of the invention, powder material is deposited onto a tape, preferably of plastics material.

In a further embodiment of the invention, the active coating is applied as a liquid. A head for applying the liquid is positioned such that the outlet or outlets of the head is less than 1mm from the surface to which the material is to be applied.

The head may be an ink jet printer head, for example an adapted Compact 200 head manufactured by Alphadot Limited. That head has 5 outlets spread over an area of about 10mm and can be used to direct liquid coating material towards the exposed surfaces of the substrate.

The liquid coating material comprises the active component and a solvent, preferably water, and an excipient, for example PEG, to aid in film forming. Preferably the solids content of the liquid coating material is very low, advantageously there would be substantially no solids content and advantageously the active material is fully dissolved in the solvent.

While it is envisaged that where the active layer is applied using an ink jet printer head, the active

material might be applied directly to a substrate from which it can be removed, it is thought that, in particular where the active material is to be peelable from the substrate in the form of a wafer, the active material would be applied to a base layer which is removable from the substrate.

For example, a first base coating layer would be applied to a substrate using the apparatus shown in Figure 2: Where the base coating material is applied to the substrate in the form of a powder material, the base coating would usually be fused to form the base coating layer. The base coating layer would be peelable from the substrate. One or more regions of active coating material would be applied to the base coating layer, for example using an ink jet printer head.

A cover coating would be applied over the active coating material. Where the cover coating is in the form of a powder, the cover coating would usually be fused to form the cover coating layer. The material would be removed from the substrate in the form of a three-layer wafer in which the active material was sandwiched between two layers. The wafer may subsequently be divided into smaller portions.

In a further embodiment of the invention, the active coating material is applied to a substrate using an ultrasonic spray head. The ultrasonic spray head forms a cloud of liquid droplets which are charged electrostatically. A charge may be imparted on the droplets, for example, by applying a high voltage to the ultrasonic spray head. The charged droplets become attracted to the substrate which is at a potential difference from the droplets.

Examples of active liquid coating materials which may be used are as follows

- 25 -

	a)	Sodium citrate	0.02
		Chlorpheniramine maleate	2.48
		Propylene glycol	4.00
		Water	18.50
5		Ethanol	75.00
	b)	Sodium citrate	0.02
		Chlorpheniramine maleate	2.00
		Methocel E15	1.00
		Lactose B.P.	6.00
10		PEG 4000	1.00
		Water	89.98

The amounts given above represent percentage by weight of each component.

The apparatus may include heating means (not shown) for drying the applied coating material. However, where the liquid coating material is such that the solvent evaporates quickly, the heater may not be required. It will be appreciated that where the heater is used the temperature required to dry the active coating will be significantly lower than the temperature required to fuse powder coating material as described above.

Figure 3 shows a further embodiment of the invention.

Figure 3 shows a schematic view of an alternative arrangement of the apparatus for producing wafers including active material.

The apparatus is similar in operation to that described above in respect of Figure 2 and comprises a stainless steel conveyor belt 31 (which may be coated with PTFE on its external surface) mounted for rotation on three rollers 34, 36. A powder hopper 32 is arranged below the conveyor 31 and wafer forming powder material is loaded into the hopper. The hopper is arranged to produce a recirculating powder bed either by fluidising the powder in the hopper with dry air or by using an auger feed screw arrangement in the hopper and vibrating the powder in the hopper.

The hopper 32 is charged to from 0.5 to 10kV either positively or negatively depending on the wafer forming powder composition to be used. For the two compositions given below, the hopper would be charged negatively.

5 A plate 33 is arranged above the portion of the conveyor belt 31 which is adjacent to the hopper 32. The plate may be a stainless steel plate and is charged to a potential difference from that of the hopper 32. The plate will normally be charged to the opposite sign to  
10 that of the hopper. The charge on the plate 33 may be from 0.1 to 10kV depending on the powder composition used and the thickness of the wafer to be formed.

The thickness of the layer formed on the surface of the belt will usually be from 0.5 to 3mm. The charge  
15 applied to the hopper and to the plate 33, and the speed of the belt will be chosen to give the desired thickness.

The powder composition is attracted to the conveyor belt 31 and adheres to the exterior surface of the belt to form a powder layer. The size of the hopper will  
20 usually be chosen so that the whole width of the conveyor belt is coated with powder. It is envisaged, however, that the powder might coat less than the whole width of the conveyor belt 31. Also, the hopper 32 may comprise a group of several hoppers each for supplying the same or  
25 different powder compositions to the conveyor belt 31. Thus the wafer produced using the apparatus may be a composite wafer in that it includes portions having different compositions. For example, the wafer might comprise a first layer including active material and a  
30 second coating layer including no active material.

As indicated above, the wafer might comprise a first layer including no active material, a second layer including active material and a third layer including no active material. That arrangement is particularly  
35 preferred because the active material is sandwiched between two outer layers which help to protect the active material from mechanical or chemical damage.

- 27 -

Such a wafer may be formed by applying a coating layer to a substrate, applying the active material to the coating layer to form an active layer and subsequently applying a cover coating layer over the active layer.

- 5 The first coating layer is removable from the substrate so that a three-layer wafer is formed.

Where reference is made herein to the active material being applied to a substrate and being removable from a substrate, it will be understood that that  
10 includes the case in which the active material is applied to a coating layer which has previously been applied to the substrate, the active coating layer being removable from the substrate together with the coating layer.

The coated portion of the conveyor belt travels from  
15 the region of the hopper to the heated roller 34. The heated roller 34 is heated to slightly above the melting point of the powder composition on the surface of the conveyor belt. As the conveyor belt moves around the heated roller 34, the powder composition on the outer  
20 surface of the conveyor belt melts and forms a fused coating on the surface of the belt.

A chilled roller 35 is arranged above the conveyor belt 31 downstream from the heated roller 34. The fused coating layer on the surface of the conveyor belt passes  
25 under the chilled roller 35 which smoothes the upper surface of the coating layer and cools the coating so that it solidifies to form a wafer on the exterior surface of the conveyor belt. It will be appreciated that other methods could be used to cool and smooth the  
30 coating layer, for example cool air jets arranged above the conveyor belt downstream from the heated roller 34.

The solidified wafer is transported on the conveyor belt 31 to the doctor blade 37 where the wafer is peeled from the surface of the belt. The conveyor belt  
35 continues around the guide rollers 36 and a further coating is deposited onto the conveyor belt as powder material moves from the hopper to the belt as described

above. Thus the apparatus can be used to produce a continuous wafer.

It is thought that the width of the conveyor belt would usually be up to 50cm. The material may be applied across the whole width of the conveyor belt. Alternatively, the material might be applied as several bands of material across the belt, the material being supplied from several separate hoppers arranged below the belt.

The wafer peeled from the conveyor passes to a cutter 38 which may be a rotary knife wafer chopper where the wafer is cut into uniform pieces. The cut wafer portions may be of any shape or size but will usually contain one dose of the active material present in the wafer. It will be appreciated that while circular or elliptical shaped wafer portions may be preferred from an aesthetic point of view, such shapes would lead to greater wastage of wafer material than, for example, rectangular-shaped wafer portions.

The pieces are then passed to a packaging station 39 where they are packaged using conventional methods to form, for example, blister packs or plasters for use as a patch on the skin.

Examples of suitable coating compositions are given above. Particularly suitable powder compositions for use with the apparatus are as follows:

Composition 1

	Diltiazem HCl (active)	50%
	Eudragit RSPO Type C	
30	(ammoniomethacrylate copolymer)	47.5%
	Titanium dioxide	2%
	Sunset yellow pigment	0.5%

The % given are % by weight. The components were mixed and the mixture was extruded and micronised to give a powder having a narrow particle size distribution below

150 $\mu$ m. For example, the particle size distribution may be as follows:

- 10% by weight less than 20 $\mu$ m
- 50% by weight less than 50 $\mu$ m
- 5 90% by weight less than 90 $\mu$ m.

Composition 2

	Diltiazem HCl	40%
	Polyethylene glycol 6000	30%
	Xylitol	20%
10	Titanium dioxide	10%

The components were wet granulated together, milled and sieved to form a powder having a narrow particle size distribution between 75 $\mu$ m and 20 $\mu$ m.

- It will be understood that other compositions
- 15 containing active material could be used. The composition will usually include from 1% to 90% by weight of active material based on the weight of the composition. The remainder of the formulation will usually comprise a polymeric matrix of binder material,
- 20 for example Eudragit E100, gelatine, PVA, PVP-PVA, PEG, lactitol, polypropylene. The compositions may additionally include plasticisers, opacifiers, disintegrants, detacifiers and/or pigments.

- The apparatus described above may be modified so
- 25 that the powder composition is deposited on a tape of material which is fed around the apparatus on the exterior surface of the conveyor, the tape having a wafer coating being removed from the apparatus. The tape may be inedible, in which case the coating material may be
- 30 removed from the tape on administration, where the active material is to be administered orally. Alternatively, the tape may be used, for example, as a patch. Where the tape is edible, the active material may be administered without removal from the tape, for example the tape and
- 35 wafer portion may be swallowed together.

Furthermore, as indicated above, the coating composition may be applied to the substrate using a different method to that described above. For example, the coating material may be applied in the form of a liquid using a head similar to that used in ink-jet printing. Alternatively, the coating material may be applied in the form of a liquid using an ultrasonic spray head. Dots of coating composition would be applied to regions of the substrate using the head.



Claims

1. A method of coating a substrate, the method including the steps of applying an active coating material to the substrate to form an active coating layer, the active coating material comprising biologically active material, wherein the active coating layer is removable from the substrate.
2. A method according to claim 1, wherein the active coating material is applied electrostatically.
- 10 3. A method according to claim 1 or claim 2, wherein the active coating material is applied in the form of a dry powder.
4. A method according to claim 3, wherein at least 90% by weight of the particles of the active coating material  
15 have a particle size between from 1 to 200 $\mu$ m.
5. A method according to any preceding claim, wherein the active coating material further includes one or more excipients.
6. A method according to any preceding claim, wherein  
20 the substrate is conveyed through a region adjacent to a source of the active coating material.
7. A method according to claim 6, wherein the method comprises supporting the substrate adjacent to the source of the active coating material with a surface of the  
25 substrate maintained at such a different electric potential from that of the active coating material that the application of the electric potential causes the active coating material to move from the source of the active coating material towards the substrate, a surface  
30 of the substrate becoming coated with the active coating material.
8. A method according to claim 6 or claim 7, wherein the substrate is supported from above and the powder moves from the source upwards towards a lower surface of  
35 the substrate.
9. A method according to any of claims 6 to 8, wherein the substrate is charged when the substrate is adjacent

to the source of the active coating material.

10. A method according to any of claims 6 to 9, wherein the source of active coating material is charged.

11. A method according to any preceding claim, wherein  
5 the method further includes the step that after the active coating layer is applied the active coating material is treated to form an active film coating secured to the surface of the substrate.

12. A method according to any preceding claim, wherein  
10 the method further includes the step of applying a cover coating layer onto the active coating layer to form a cover coating layer such that the active coating layer is substantially completely covered by the cover coating layer.

13. A method according to claim 12, wherein the cover coating layer is removable from the substrate.

14. A method according to any preceding claim, wherein the active coating material is applied to a part of a surface of the substrate, the active coating layer  
20 forming a first active coated region on the surface of the substrate.

15. A method according to any preceding claim, wherein the method includes the further step of applying a second active coating layer onto a surface of the substrate, the  
25 second active coating layer forming a second active coating region on a surface of the substrate.

16. A method according to claim 15, wherein the method further includes the step of applying a second cover coating layer onto the second active coating layer to  
30 form a second cover coating layer such that the second active coating layer is substantially completely covered by the second cover coating layer, the second cover coating layer being substantially separate from the first cover coating layer.

17. A method of coating a plurality of coating regions  
35 onto the surface of a substrate, the method comprising the steps of:

(a) applying active coating material to a surface of the substrate to form a plurality of active coating regions on the surface comprising active coating layers, the active coating material including biologically active material

(b) applying cover coating material to a surface of the substrate to form a plurality of cover coating regions, the cover coating regions forming layers of cover coating material, each active coating region being substantially completely covered by a cover coating region,

such that each region of active coating and cover coating is removable from the surface of the substrate.

18. A method according to any preceding claim, the method further including the step of removing the active coating layer from the substrate to form a wafer comprising active material.

19. A method according to claim 18, wherein the wafer is cut to form wafer portions, each wafer portion including substantially a dose of the active material.

20. Apparatus for coating a pharmaceutical substrate according to a method as claimed in any of claims 1 to 19.

21. An apparatus for coating a substrate, the apparatus comprising:

(a) a source of active coating material,

(b) support means for supporting a substrate adjacent to the source of the active coating material such that the active coating material forms an active coating layer on the surface of the substrate.

22. An apparatus according to claim 21, further comprising:

(c) a source of a cover coating material,

(d) means for conveying the substrate having the active coating layer to a position adjacent to the source of cover coating material such that the cover coating material forms a cover coating layer which substantially

completely covers the active coating layer.

23. An apparatus according to claim 21 or claim 22, wherein the substrate comprises a conveyor belt.

24. An apparatus according to any of claims 21 to 23,  
5 further including means for applying a charge to the source of active coating material.

25. An apparatus according to any of claims 21 to 24, wherein the apparatus further includes means for applying a charge to the substrate.

10 26. An apparatus according to any of claims 21 to 25, wherein the source is arranged below the substrate.

27. An apparatus for coating a substrate, the apparatus comprising:

(a) a source of active coating material  
15 (b) means for moving the substrate relative to the source of coating material,

(c) means for applying an active coating material onto a surface of the substrate to form a plurality of active coating regions

20 (d) means for applying a cover coating material onto the surface of the substrate to form a plurality of cover coating regions such that each active coating region is substantially completely covered by a cover coating region,

25 the coating materials being applied such that the active coating material is removable from the surface of the substrate.

28. A coated substrate comprising an active coating layer on a surface of the substrate, the active coating  
30 layer including biologically active material and in which the active coating layer is removable from the surface of the coated substrate.

29. A coated substrate according to claim 28, the substrate further including a cover coating layer on a  
35 surface of the substrate, the cover coating layer substantially completely covering the active coating layer in which the cover coating layer is removable from

the surface of the substrate.

30. A coated substrate according to claim 28 or claim 29, wherein the substrate includes a plurality of active coating layers forming active coating regions on a surface of the substrate.

31. A coated substrate according to claim 30, wherein each active coating region includes a cover coating region comprising a layer of cover coating material in which each active coating region is substantially completely covered by a cover coating region.

32. A coated substrate when made according to a method as claimed in claims 1 to 17.

33. An intermediate product for use in producing a plurality of solid dosage forms, the intermediate product comprising a substrate and an active coating layer deposited on the substrate, the amount of active coating material deposited on a given area of the substrate being controlled such that the product can subsequently be divided into portions with each portion containing a predetermined amount of active coating material, each predetermined amount being one dose of the active material.

34. A wafer for administration to a patient, the wafer comprising biologically active material and having a thickness of less than 2mm.

35. A wafer produced by a method according to claim 18 or claim 19.

36. A method of coating a substrate, the method comprising applying an active coating material to a surface of the substrate to form an active coating layer, the active coating material comprising biologically active material, applying a cover coating layer over the exposed surfaces of the active coating layer and dividing the layered product to form layered portions, each layered portion including substantially one dose of the active material.

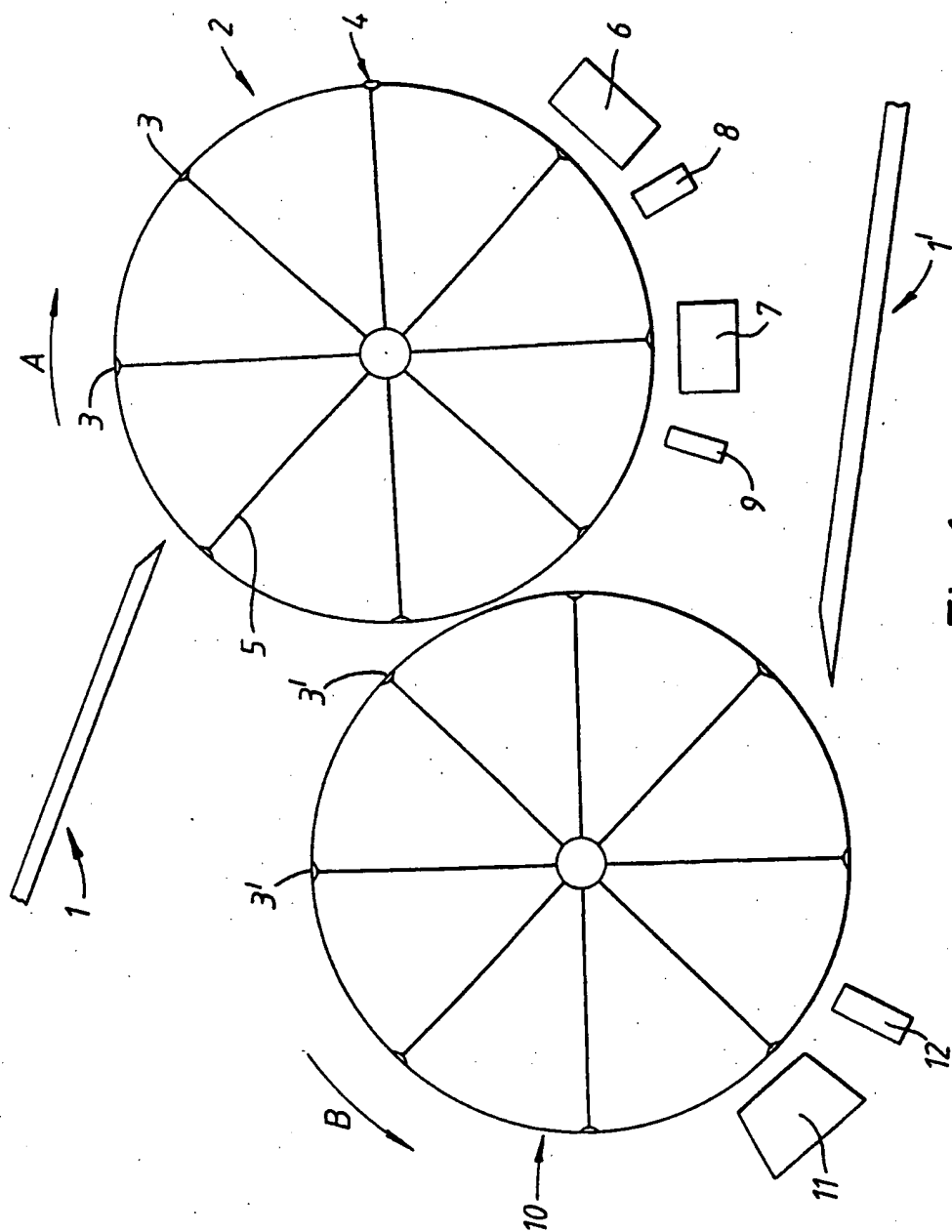
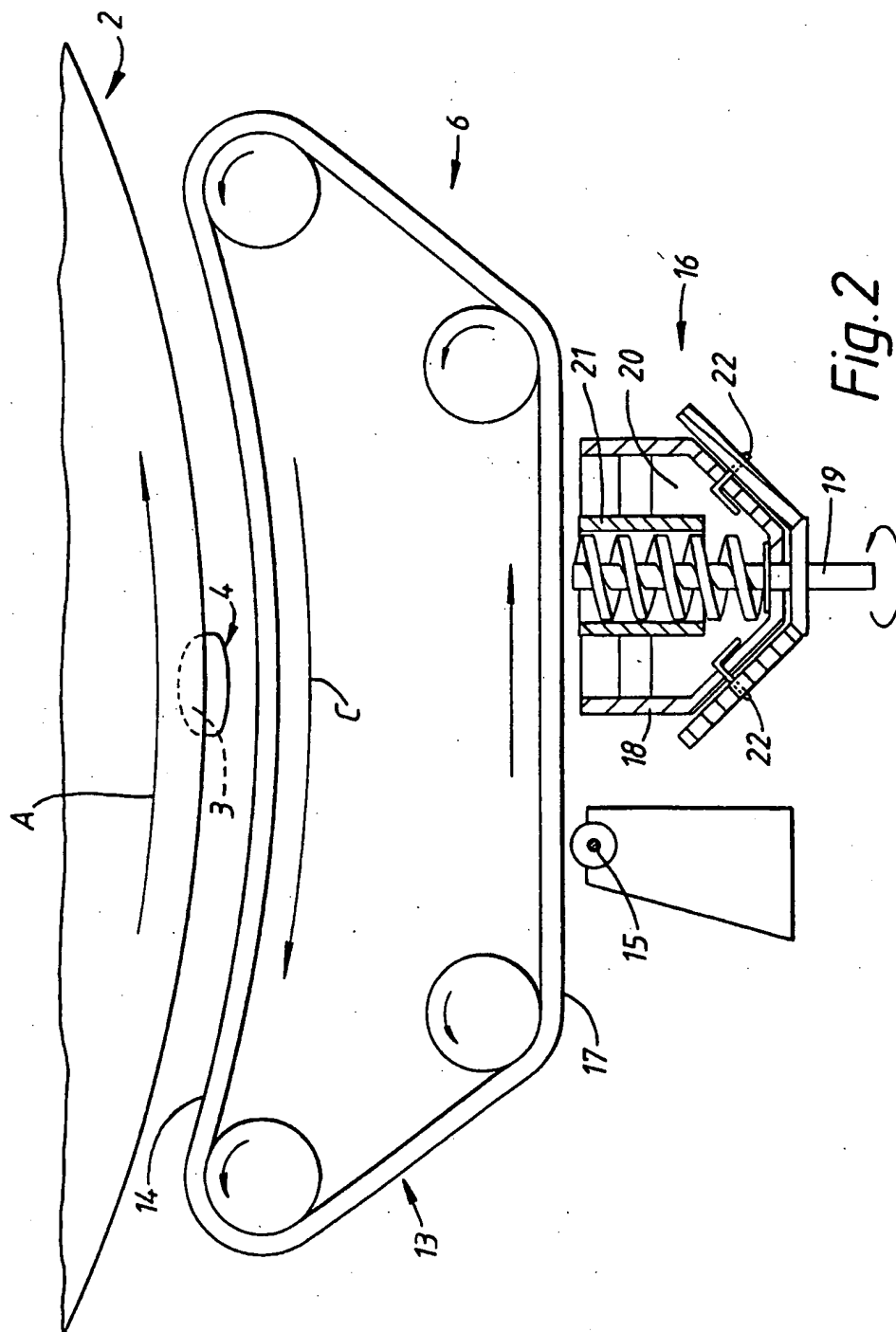
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Fig. 1

2/3



3/3

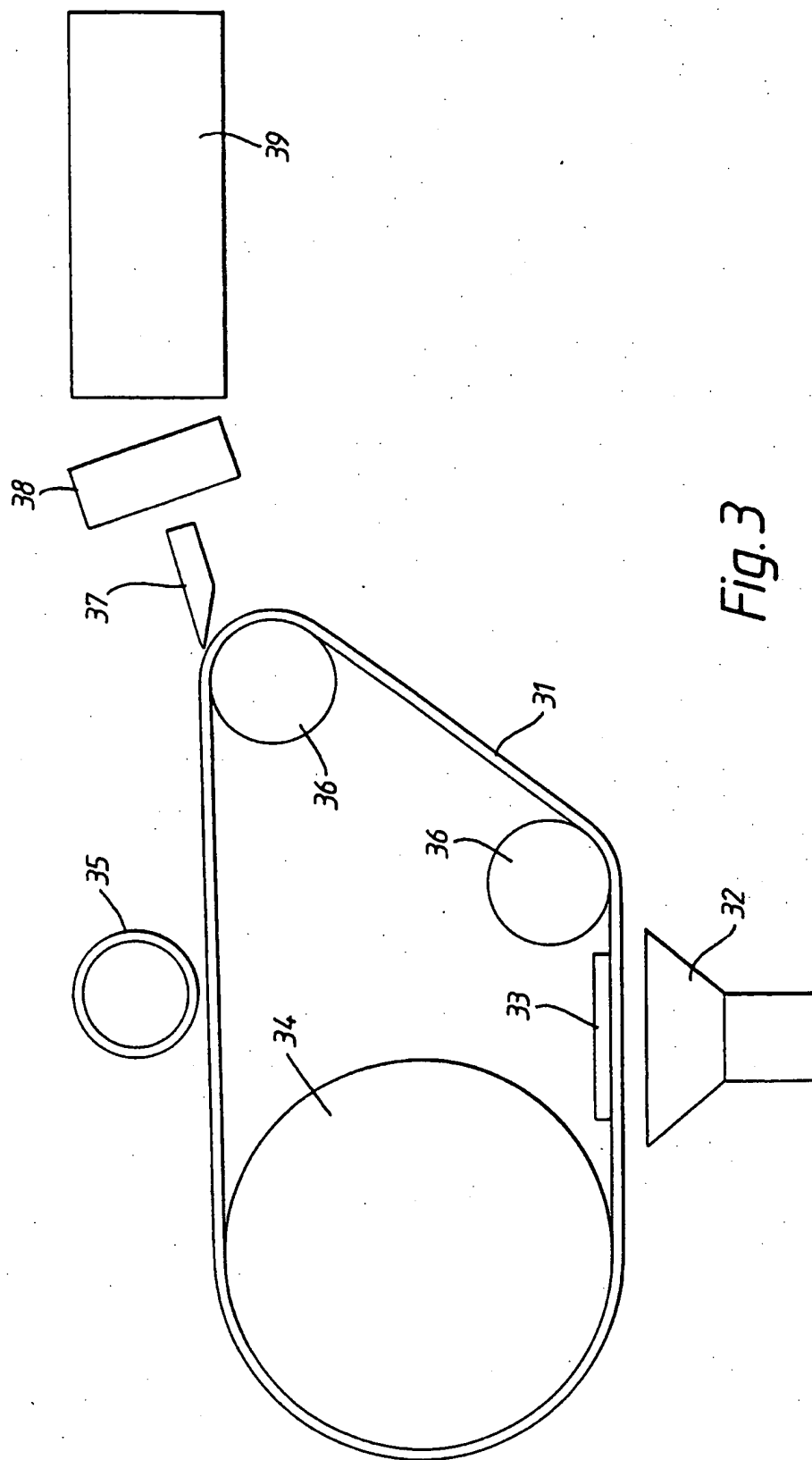


Fig. 3



# INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/GB 97/03113

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 259 749 A (DESITIN ARZNEIMITTEL GMBH) 16 March 1988  see the whole document ---	1,5, 11-13, 18-21, 28,29, 32-36
X	LU 52 460 A (ASTRA PHARMACEUTICAL PRODUCTS, INC.) 25 June 1968  see page 4, line 3 - page 5, line 23 see page 12, line 19 - page 16, line 3 see page 26, line 26 - page 27, line 4 --- -/--	1,5, 11-13, 20,28, 29,32

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/03113

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1 561 100 A (F. HOFFMANN-LA ROCHE & CO. AKTIENGESELLSCHAFT) 13 February 1980 see page 1, line 5 - line 15 see page 12, line 39 - page 13, line 27 ----	1-36
T	WO 96 35413 A (BERWIND PHARMACEUTICAL SERVICES INC.) 14 November 1996 see page 18, line 28 - page 19, line 18 see page 21, line 8 - line 14 see page 23, line 13 - line 29 see claims 30-34 see the whole document ----	1-36
X	WO 91 16041 A (SMITH KLINE & FRENCH LABORATORIES LIMITED) 31 October 1991 see the whole document -----	34

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/03113

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 259749 A	16-03-88	DE 3630603 A	10-03-88
		AU 601478 B	13-09-90
		AU 7792987 A	17-03-88
		CA 1313497 A	09-02-93
		DE 3772136 A	19-09-91
		JP 2620789 B	18-06-97
		JP 63077816 A	08-04-88
		US 4925670 A	15-05-90
LU 52460 A	25-06-68	BE 690383 A	29-05-67
		DE 1617282 A	06-02-75
		DK 118841 B	12-10-70
		FR 6733 M	24-02-69
		GB 1108837 A	
		NL 6616878 A	31-05-67
GB 1561100 A	13-02-80	US 4029758 A	14-06-77
		US 4029757 A	14-06-77
		US 4031200 A	21-06-77
		AT 365449 B	11-01-82
		CA 1085295 A	09-09-80
		CH 624846 A	31-08-81
		DE 2656387 A	30-06-77
		DK 562276 A, B,	16-06-77
		FI 763597 A	16-06-77
		FR 2335206 A	15-07-77
		JP 1395182 C	11-08-87
		JP 52076419 A	27-06-77
		JP 62000125 B	06-01-87
		LU 76378 A	18-01-78
		NL 7613922 A, B,	17-06-77
		SE 438597 B	29-04-85
		SE 7614123 A	25-08-77
		US 4072551 A	07-02-78
		US 4126502 A	21-11-78
		ZA 7607136 A	26-10-77
		US 4126503 A	21-11-78
		AU 2051976 A	22-06-78
		US 4083741 A	11-04-78
		US 4307555 A	29-12-81

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/03113

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1561100 A		US 4349531 A	14-09-82
		US 4165998 A	28-08-79
		US 4069084 A	17-01-78
		US 4069086 A	17-01-78
		AU 514195 B	29-01-81
		BE 849377 A	14-06-77
		CA 1087974 A	21-10-80
		US 4128445 A	05-12-78
		US 4197289 A	08-04-80
		US 4332789 A	01-06-82
		US 4128444 A	05-12-78
WO 9635413 A	14-11-96	AU 5655196 A	29-11-96
		AU 5655296 A	29-11-96
		EP 0824344 A	25-02-98
		WO 9635516 A	14-11-96
		GB 2316086 A	18-02-98
		GB 2316342 A	25-02-98
		NO 975131 A	09-01-98
		NO 975132 A	09-01-98
WO 9116041 A	31-10-91	AT 131383 T	15-12-95
		AU 649041 B	12-05-94
		AU 7748191 A	11-11-91
		CA 2081109 A	27-10-91
		DE 69115476 D	25-01-96
		DE 69115476 T	05-06-96
		EP 0526524 A	10-02-93
		ES 2080314 T	01-02-96